HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2022 February 25.

Published in final edited form as:

Clin Infect Dis. 2021 November 02; 73(9): e2799–e2806. doi:10.1093/cid/ciaa1218.

Respiratory Illness Caused by *Corynebacterium diphtheriae* and *C. ulcerans*, and Use of Diphtheria Antitoxin in the United States, 1996–2018

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Abstract

Background.—Respiratory diphtheria is a toxin-mediated disease caused by *Corynebacterium diphtheriae*. Diphtheria-like illness, clinically indistinguishable from diphtheria, is caused by *Corynebacterium ulcerans*, a zoonotic bacterium that can also produce diphtheria toxin. In the United States, respiratory diphtheria is nationally notifiable: specimens from suspected cases are submitted to the Centers for Disease Control and Prevention (CDC) for species and toxin confirmation, and diphtheria antitoxin (DAT) is obtained from CDC for treatment. We summarize the epidemiology of respiratory diphtheria and diphtheria-like illness and describe DAT use during 1996–2018 in the United States.

Methods.—We described respiratory diphtheria cases reported to the National Notifiable Diseases Surveillance System (NNDSS) and *C. ulcerans*-related diphtheria-like illness identified through specimen submissions to CDC during 1996–2018. We reviewed DAT requests from 1997 to 2018.

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Results.—From 1996 to 2018, 14 respiratory diphtheria cases were reported to NNDSS. Among these 14 cases, 1 was toxigenic and 3 were nontoxigenic *C. diphtheriae* by culture and Elek, 6 were culture-negative but polymerase chain reaction (PCR)-positive for diphtheria toxin gene, 1 was culture-positive without further testing, and the remaining 3 were either not tested or tested negative. Five cases of respiratory diphtheria-like illness caused by toxigenic *C. ulcerans* were identified. DAT was requested by healthcare providers for 151 suspected diphtheria cases between 1997 and 2018, with an average of 11 requests per year from 1997 to 2007, and 3 per year from 2008 to 2018.

Conclusions.—Respiratory diphtheria remains rare in the United States, and requests for DAT have declined. Incidental identification of *C. ulcerans*-related diphtheria-like illness suggests surveillance of this condition might be warranted.

Keywords

diphtheria; diphtheria-like illness; *Corynebacterium diphtheriae* ; *Corynebacterium ulcerans* ; toxin-producing

Respiratory diphtheria is a life-threatening bacterial disease caused by toxin-producing strains of *Corynebacterium diphtheriae*. Once a major cause of childhood morbidity and mortality worldwide, respiratory diphtheria is now rare in countries with high coverage of diphtheria toxoid-containing vaccine (DTCV) [1, 2]. Incidence in the United States has decreased from >100 cases per 100 000 persons in the 1920s to <0.01 case per 100 000 persons from 1980 to 1995 [3, 4]. Similarly, global diphtheria disease burden has declined by more than 80%, from 97 511 reported cases in 1980 to 16 651 cases in 2018 [5]. However, the recent occurrence of a number of worldwide outbreaks is a reminder that although rare, respiratory diphtheria remains a public health threat, causing substantial morbidity among unprotected populations [6–9].

Two zoonotic *Corynebacterium* species, *C. pseudotuberculosis* and *C. ulcerans*, can also produce diphtheria toxin and associated disease in humans. *C. pseudotuberculosis* causes lymphadenopathy and suppurative infections in sheep, goats, and cattle; transmission to humans through exposure of open wounds or ingestion of contaminated raw milk results in fever and suppurative lymphadenitis [10]. *C. ulcerans* causes mastitis in cattle and respiratory infections in other animals and can spread to humans through close contact with secretions [11–14]. In humans, toxigenic *C. ulcerans* can cause cutaneous and respiratory illnesses, which are clinically indistinguishable from diphtheria [15–20]. Person-to-person transmission of *C. ulcerans*, although possible, has not been conclusively established [18, 21].

The cornerstone of treatment of suspected respiratory diphtheria is early administration of diphtheria antitoxin (DAT), which can prevent life-threatening complications [1]. DAT is currently produced using serum from horses that are hyperimmunized with diphtheria toxoid, and there is a global shortage of equine DAT due to high manufacturing costs and previously low demand [22]. A Food and Drug Administration (FDA)-licensed DAT product has not been available in the United States since 1996. However, beginning in 1997, physicians have been able to access an unlicensed DAT product from the CDC through

an FDA-approved Investigational New Drug (IND) protocol for emergency treatment of suspected diphtheria cases [23, 24].

In this report, we summarize the epidemiology of respiratory diphtheria in the United States reported from 1996 to 2018; we also describe cases of respiratory diphtheria-like illness caused by *C. ulcerans* identified during this time. Additionally, we review use of DAT for suspected diphtheria cases from 1997 to 2018, the time period it has been available through an IND.

METHODS

Diphtheria is a nationally notifiable disease in the United States [20]. Suspected cases are investigated by local or state health authorities, and those that meet the Council of State and Territorial Epidemiologists (CSTE) case definitions for diphtheria are reported to the National Notifiable Disease Surveillance System (NNDSS). Cases reported to NNDSS from 1996 through 2018 were included in the analysis. Cases were classified as probable or confirmed according to the CSTE case definitions used during that period [25]. A confirmed case was defined as an upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx (clinical case) and either isolation of *C. diphtheriae* from the nose or throat, histopathologic diagnosis of diphtheria, or epidemiologic linkage to a laboratory-confirmed case of diphtheria. A probable case was defined as a clinical case with no laboratory confirmation and no epidemiologic linkage to a laboratory-confirmed case. Clinical specimens and isolates from suspected diphtheria cases were sent to the Pertussis and Diphtheria Laboratory at CDC for characterization and confirmation.

Diphtheria-like disease caused by *C. ulcerans* is not notifiable in the United States. However, CDC should receive specimens and case investigation data from all suspected diphtheria cases, including those caused by *C. ulcerans*, for confirmation of species and toxin production. This review also included analysis of suspected respiratory diphtheria cases from 1996 to 2018 for which toxin-producing *C. ulcerans* was confirmed as the cause.

DAT became available as part of a CDC-held IND protocol for diphtheria treatment in 1997; product was manufactured by Pasteur Merieux (France, available 1997–2004) or Instituto Butantan (Brazil, 2004–present) [23, 24]. When requesting DAT for treatment of suspected cases of diphtheria, healthcare providers are required to submit a completed diphtheria case investigation worksheet [26]. We evaluated DAT utilization and characteristics of patients who received DAT from 1997 to 2018.

Laboratory Methods

Clinical specimens collected from suspected diphtheria cases, including throat and nasal swabs and/or pieces of pseudomembranes, were sent to CDC for confirmatory testing. Specimens were cultured on blood and Tinsdale agars; for those black colonies with halos on Tinsdale agar, *Cornyebacterium* species was identified using the API Coryne kit (bioMérieux, Durham, NC, USA) as described previously [27]. The Elek test was performed to confirm toxin production when *C. diphtheriae* or *C. ulcerans* were isolated [28]. DNA was extracted from clinical specimens or isolates and tested with conventional

or real-time PCR to detect A and B subunits of the diphtheria toxin gene (*tox*) [29, 30]. PCR results were considered positive if either of the 2 targets (A or B subunits) for *tox* were reproducibly positive [29–31]. Prior to 2018, these PCR assays were not able to determine *Corynebacterium* species; if culture was unavailable or negative, then the causative bacteria could not be identified with certainty and was presumed to be 1 of 3 species known to harbor *tox: C. diphtheriae, C. ulcerans*, or *C. pseudotuberculosis*. Further information on these PCR assays is available in the Supplementary Material.

Analysis

Data were compiled in Microsoft Excel and descriptive analyses were performed using SAS version 9.3 (SAS Institute Inc. Cary, NC, USA). Where possible, data were presented in aggregate to protect identity. This review was determined to be nonresearch, public health practice, and did not require Institutional Review Board approval.

RESULTS

Respiratory Diphtheria

During 1996–2018, a total of 14 respiratory diphtheria cases were reported to NNDSS, of which 43% (6/14) met the CSTE definition for a confirmed case, and 57% (8/14) were classified as probable (Figure 1, Table 1). The 14 cases were reported from 10 states, spread across 7 of the 10 geographic regions designated by the US Department of Health and Human Services [32]. Patient age ranged from 8 months to 86 years; 86% (12/14) were aged ≥15 years. The majority of patients were female (64%, 9/14). Sixty-four percent (9/14) of patients were White, 14% (2/14) were Native American, 7% (1/14) were Asian or Pacific Islander, 7% (1/14) were other race, and 7% (1/14) had unknown race; 21% (3/14) were Hispanic or Latino. Among the 64% (9/14) of patients with known vaccination status, 44% (4/9) were up-to-date with DTCV (according to recommendations by the Advisory Committee on Immunization Practices [ACIP]), 44% (4/9) were partially vaccinated but not up-to-date with DTCV, and 11% (1/9) were unvaccinated.

Specimens from 11 of the 14 patients were sent to CDC; of the remaining 3, 1 was determined to be culture-positive external to CDC but specimen was not shared, and 2 were either not shared or not collected (Table 1, Supplementary Figure). Of those sent to CDC, 4 grew *C. diphtheriae* in culture, including 1 that was toxin-producing and 3 that were non-toxin-producing by Elek test. The remaining 7 did not grow *C. diphtheriae* in culture and were therefore unable to be tested for toxigenicity. Of these 7 specimens, 6 tested positive and 1 tested negative for *tox* by PCR; *Corynebacterium* species was not able to be identified for these.

Of the 14 reported diphtheria cases, 1 patient died. The fatality was a 63-year-old unvaccinated man who had visited Haiti, a diphtheria-endemic country, within the 6 weeks prior to onset of symptoms [33]. Although culture-negative for *C. diphtheriae*, this imported case was reported as confirmed based on classic diphtheria symptoms and signs, demonstration of gram-positive rods from a throat swab specimen, a positive PCR test for

tox, no history of vaccination with DTCV, high probability of recent exposure in a country with endemic diphtheria, and illness onset while returning to the United States.

Five of the 14 patients (36%), including the fatality, were treated with DAT; the remaining 9 patients (64%) did not request DAT. Of those patients who were treated with DAT, specimens from 3 were culture-negative for *C. diphtheriae* but positive for *tox* by PCR, 1 was negative by culture and PCR, and 1 grew non-toxigenic *C. diphtheriae*. All 14 diphtheria patients received antibiotic treatment with either penicillin or erythromycin.

Respiratory Diphtheria-like Illness Caused by *C. Ulcerans*

During 1996–2018, specimens from 5 cases of suspected respiratory diphtheria were tested at CDC and found to be culture-positive for *C. ulcerans*; toxin production was confirmed by Elek test on all isolates (Table 2). Patient age ranged from 4 to 85 years, and all presented with the classical pseudomembrane of respiratory diphtheria. Two patients died; neither received DAT. The remaining 3 patients who survived received DAT. All patients were either unvaccinated or were not up to date with DTCV booster doses.

Case investigations did not establish route of transmission: 2 patients had opportunity for animal exposure, whereas the remaining cases were without known exposure. All patients denied consumption of unpasteurized milk products, travel outside the United States, or contact with international travelers during the previous month.

Diphtheria Antitoxin

CDC released DAT for the treatment of 151 patients with suspected respiratory diphtheria between 1997 and 2018 (Figure 2). During this period, there was a decreasing number of DAT releases: over 80% of releases occurred in the first 11 years (1997–2007), with an average of 11 releases per year during this time, compared with approximately 3 releases per year during 2008–2018. DAT was administered to 68% (103/151) of patients; 32% (48/151) did not receive DAT because their healthcare providers later decided the diagnosis of diphtheria was unlikely. Among the 103 patients who received DAT, 5 met the CSTE case definition for diphtheria (included among the 14 reported cases noted in this report), and 2 had confirmed *C. ulcerans* diphtheria-like illness (also noted in this report). The third *C. ulcerans* patient who received DAT received it prior to implementation of the IND, in 1996, and so is not included in the analysis of DAT use. CDC ruled out diphtheria by culture and PCR testing for 93% (96/103) of patients who received DAT. Etiology was undocumented for 31% (30/96) of these patients, although other final diagnoses included streptococcal pharyngitis, viral/undetermined pharyngitis, herpes simplex virus infection, candidiasis infection, Stevens-Johnson syndrome, leukemia, lymphoma, vancomycin-resistant enterococcal infection, methicillin-resistant *Staphylococcus aureus* infection, human immunodeficiency virus (HIV)/pneumocystis pneumonia, and infectious mononucleosis.

DISCUSSION

Our review of national diphtheria surveillance data indicates that the incidence of diphtheria has remained very low over the last 23 years, especially in people <15 years of age,

highlighting the success of the childhood vaccination program in the United States. This report also revealed that the number of healthcare provider requests for DAT has decreased, commensurate with the low disease incidence. Notably, some of the suspected respiratory diphtheria cases during this period were determined to be diphtheria-like illness caused by *C. ulcerans*.

In comparison to the 41 respiratory diphtheria cases reported from 1980 to 1995, only 4 cases were reported between 2003 and 2018 [4]. Of note, at least 3 of the 6 confirmed cases in this report were due to non-toxigenic strains of *C. diphtheriae*. Between 1980 and 2018, the CSTE case definition did not require confirmation of toxin production; therefore, national reporting included cases caused by both non-toxigenic and toxigenic *C. diphtheriae*. This may have inflated the true burden of respiratory diphtheria over the last 39 years. For example, only a single case reported during the current analysis period and only a third (13/41) of cases reported from 1980 to 1995 were confirmed to be toxin-producing [4]. Additionally, *Corynebacterium* species was not identified in 7 cases for which culture was negative; although *tox* was positive by PCR for 6, limitations of the available assay did not allow species identification. These cases met the clinical criteria for respiratory diphtheria; however, disease could have been caused by *C. ulcerans* or *C. pseudotuberculosis*, instead of *C. diphtheriae*, potentially contributing to an overestimation of disease burden. Beginning in 2019, the case definition has been revised to include only disease caused by toxigenic *C. diphtheriae* [34]. In addition, because transmission of toxigenic diphtheria from nonrespiratory sites, such as skin, can result in respiratory infection in susceptible individuals, the new definition was expanded to include reporting of toxigenic *C. diphtheriae* infection from any anatomic site, not only respiratory.

The last imported case of respiratory diphtheria in the United States occurred in 2003 [33]. However, ongoing surveillance of toxigenic *C. diphtheriae* remains critical because diphtheria is endemic in countries with inadequate vaccination coverage, and outbreaks recently have been reported in the Americas, Asia, Yemen, and South Africa [6–9, 35–41]. Given reports of imported travel-related diphtheria in developed countries with high vaccination coverage, continued surveillance in the United States is needed for appropriate public health action [42, 43]. Furthermore, there are concerns that current immunity levels among adults are not sufficient to protect against diphtheria disease. DTCV immunity wanes over time, and booster doses are required to maintain lifelong protection. In the United States, a 3-dose DCTV primary series and 2 subsequent booster doses through childhood are recommended, followed by DCTV decennial booster doses beginning in adolescence [44]. In 2017, 88.7% of adolescents 13–17 years of age had been vaccinated with a DTCV booster dose, whereas 63.4% of adults aged ≥19 years reported receipt of a tetanus toxoid or tetanus and diphtheria toxoid-containing vaccine in the preceding 10 years [45, 46]. Persistently low rates of booster dose vaccination can leave large proportions of US adults susceptible to diphtheria and increase the possibility of outbreaks, highlighting again the need for ongoing surveillance. Finally, *C. diphtheriae* can circulate for decades among undervaccinated or underserved populations. For example, molecular evidence indicates that closely related *C. diphtheriae* strains have persisted in 2 populations in the United States and Canada for more than 20 years [47, 48]. These findings suggest that undervaccinated populations remain at

risk because of continued circulation of toxigenic *C. diphtheriae*, even if overall vaccination coverage is high.

The burden of respiratory diphtheria in the United States appears to be lower than that of other countries with similar DCTV vaccination schedules, vaccination coverage, and population size. Member states of the European Centre for Disease Control (ECDC) reported a total of 4–10 annual cases of respiratory diphtheria caused by toxigenic *C. diphtheriae* from 2014 to 2017 [49–52]. One reason for the difference in disease burden could be stringency of the case definitions employed: the ECDC clinical case definition includes a "mild respiratory disease" classification that does not require presence of pseudomembrane and therefore may be inclusive of mild cases that the United States would not report. In addition, respiratory diphtheria disease burden for the ECDC reporting region appears to be driven by endemic disease in Latvia, with sporadic or travel-related cases elsewhere; in the United States, reported cases have been sporadicover the last 23 years [49–52]. Although underreporting of respiratory diphtheria is another possible explanation for the difference in disease burden between the United States and other countries, we think this is unlikely. Surveillance in the United States is uniform, with a nationally implemented case definition, and culture capacity is generally available throughout the country; CDC provides Elek and PCR testing for all detected *C. diphtheriae* isolates [3, 53]. In fact, testing of *C. diphtheriae* isolates has increased over time, providing reassurance that lack of testing is not responsible for the lower burden of reported disease in the United States. During 1996–2011, an average of 4 isolates was confirmed by CDC as *C. diphtheriae* annually; this increased 10-fold to 40 per year during 2012–2018. However, >50% of isolates were of cutaneous origin, and few were toxigenic. Of the 339 *C. diphtheriae* isolates submitted to CDC from 1996 to 2018, 13 (4%) were toxigenic: 1 respiratory (1996 case identified in this report), 4 cutaneous, and 8 from asymptomatic carriers that did not meet clinical criteria for reporting (CDC, unpublished data). This overall increase in testing may be due to rising use of matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry (MALDI-TOF) as an initial diagnostic tool for identification of *C. diphtheriae* in addition to increased awareness of cutaneous diphtheria [54]. We also believe clinical under-recognition of respiratory diphtheria is unlikely, as our findings suggest that US healthcare providers are more likely to over-diagnose this disease: CDC ruled out toxigenic *C. diphtheriae* for 93% of suspected patients who received DAT.

Although disease caused by toxigenic *C. ulcerans* is not nationally reportable, 5 cases caused by this bacterium were incidentally captured by surveillance because of the diphtheria-like illness they caused [15–17, 19]. Worldwide, there have also been reports of *C. ulcerans*-related disease, although most cases have been associated with direct exposure to animals either infected or colonized with *C. ulcerans* [11–14]. Interestingly, a source of infection was not firmly established for the US. cases; human-to-human transmission of *C. ulcerans* has not been verified for these cases or others [15–17, 19]. *C. ulcerans* is not considered a vaccine-preventable disease, but data suggest that vaccination with diphtheria toxoid could protect against development of disease, as studies have shown that DAT inhibits *C. ulcerans* toxin in vitro [55, 56]. If identification of *C. ulcerans* cases in the United States increases, systematic surveillance may be considered; multiple countries including those of ECDC, Canada, and Australia already include toxigenic *C. ulcerans* in their case definition

[57–59]. However, further investigations may be needed to confirm the effectiveness of vaccination and DAT in preventing and treating disease, as well as to confirm mechanisms of transmission.

Use of DAT in the United States continues, but the frequency of DAT releases has declined over time, with an average of 3 releases per year during 2008–2018. For suspected diphtheria cases, early treatment with DAT is recommended without awaiting laboratory confirmation, in order to prevent severe disease and death; however, the current epidemiology and likelihood of exposure should be considered before requesting and administering DAT. This should also be balanced with the knowledge that there is a limited supply of DAT globally, as well as the fact that DAT is an equine product, and its use may be associated with rare anaphylactic reactions [22, 26, 60]. Consultation with subject matter experts at state health departments and CDC is required prior to requesting DAT [61].

In summary, respiratory diphtheria remains rare in the United States, but ongoing disease surveillance is critical to rapidly identify cases and prevent further transmission that may occur secondary to disease importation, susceptibility among adults, and continued circulation of *C. diphtheriae* strains in some US populations. Identification of toxigenic *C. ulcerans* in the United States is also rare but may warrant further investigation and surveillance in the future, especially if detection increases. In line with the decreasing reported diphtheria disease, requests for DAT treatment have also declined in the United States, but judicious use should be promoted given the global shortage of product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial support.

This work was supported by Centers for Disease Control and Prevention.

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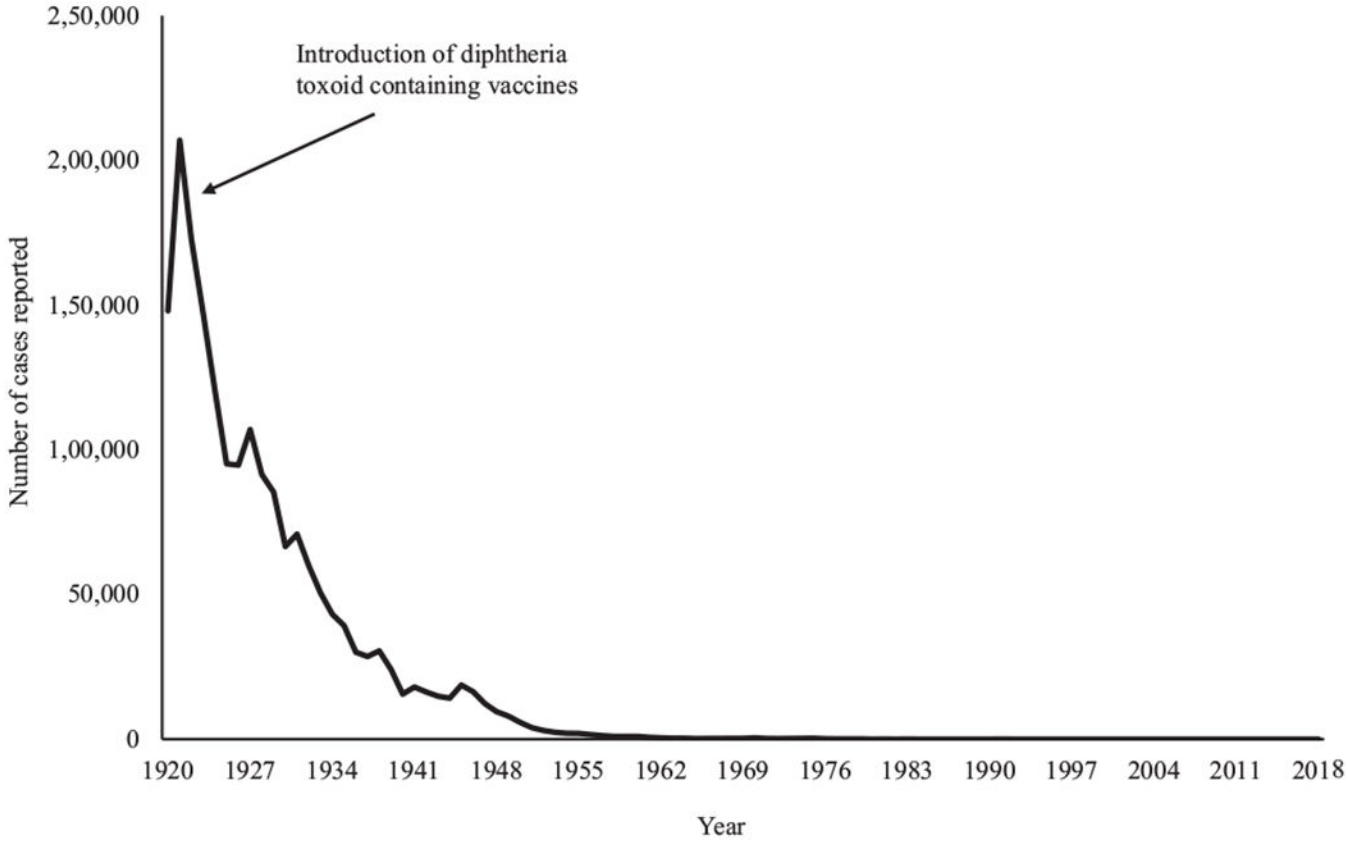

Figure 1.

Reported cases of diphtheria in the United States, 1920–2018. Graph depicts number of cases reported to the National Notifiable Diseases Surveillance System, by year. The arrow represents the timeframe of diphtheria toxoid-containing vaccine introduction.

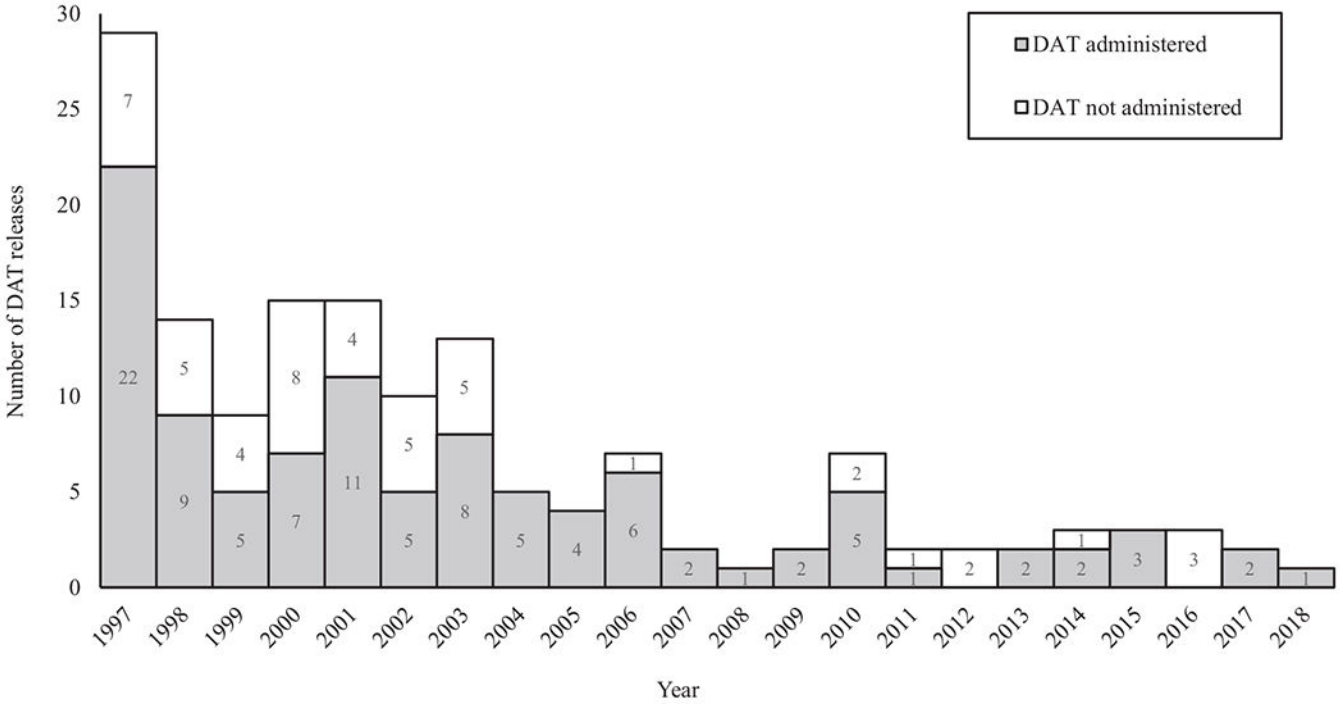

Figure 2.

Annual release and administration of DAT for treatment of suspected diphtheria in the United States, 1997–2018. The gray bar represents requests for DAT in which it was administered; the number of such is indicated within the bar. The blank bar represents requests for DAT in which it was not administered; the number of such is indicated within the bar. Abbreviation: DAT, diphtheria antitoxin.

Table 1.

Characteristics of Patients with Respiratory Diphtheria Reported to Nationally Notifiable Diseases Surveillance System, United States, 1996–2018

			Laboratory Test Results						
Reporting Year	**Age (years)**	**Case Classification**	**Culture**	**Elek test[a]**	**PCR, *tox* Gene[b]**	**Vaccination Status[c]**	**Exposure**	**DAT Received**	**Outcome**
1996	≥15	Probable	Not done	Not done	Not done	Unknown	Unknown	No	Survived
1997	≥15	Probable	Negative	…	Positive	Unknown	Unknown	No	Survived
1997	<15	Probable	Negative	…	Positive	Unknown	Unknown	No	Survived
1997	≥15	Confirmed	Positive *C. diphtheriae*	Non-toxigenic	Negative	Vaccinated	Unknown	Yes	Survived
1997	≥15	Confirmed	Positive *C. diphtheriae*	Toxigenic	Positive	Vaccinated	Unknown	No	Survived
1998	≥15	Probable	Negative	…	Positive	Partially vaccinated	Unknown	Yes	Survived
2000	≥15	Confirmed	Positive *C. diphtheriae*	Not done	Not done	Unknown	Unknown	No	Survived
2001	≥15	Probable	Negative	…	Positive	Partially vaccinated	Unknown	Yes	Survived
2001	≥15	Probable	Negative	…	Negative	Unknown	Unknown	Yes	Survived
2002	≥15	Probable	Not done	Not done	Not done	Partially vaccinated	Exposure to travelers from Eastern Europe and Australia	No	Survived
2003	≥15	Confirmed	Negative	…	Positive	Unvaccinated	International travel to Haiti	Yes	Deceased
2012	≥15	Probable	Negative	…	Positive	Partially vaccinated	Unknown	No	Survived
2014	≥15	Confirmed	Positive *C. diphtheriae*	Non-toxigenic	Negative	Vaccinated	Unknown	No	Survived
2018	<15	Confirmed	Positive *C. diphtheriae*	Non-toxigenic	Negative	Vaccinated	Unknown	No	Survived

Unvaccinated: no DTCV received.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; DAT, diphtheria antitoxin; DTCV, diphtheria toxoid-containing vaccine; PCR, polymerase chain reaction.

[a] Elek test only possible if *C. diphtheriae* isolate available.

[b] Conventional or real-time PCR.

[c] Vaccination status.

Vaccinated: age-appropriate DTCV received according to ACIP recommendations, including adult decennial booster doses.

Partially vaccinated: received at least 1 dose of DTCV but not up-to-date according to ACIP recommendations.

Table 2.

Characteristics of Patients with Diphtheria-like Illness Caused by Toxigenic[a] *C. ulcerans*, United States, 1996–2018

Reporting Year	Age (years)	Vaccination Status[b]	Exposure	DAT Received	Outcome
1996	≥15	Unvaccinated	Unknown	Yes	Survived
1999	≥15	Partially vaccinated	Unknown	No	Deceased
2005	≥15	Partially vaccinated	Unknown	Yes	Survived
2010	≥15	Partially vaccinated	Unknown	Yes	Survived
2010	≥15	Partially vaccinated	Unknown	No	Deceased

Unvaccinated: no DTCV received.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; DAT, diphtheria antitoxin; DTCV, diphtheria toxoid-containing vaccine; PCR, polymerase chain reaction.

[a]Confirmed by Elek test and conventional or real-time PCR.

[b]Vaccination status.

Vaccinated: age-appropriate DTCV received according to ACIP recommendations, including adult decennial booster doses.

Partially vaccinated: received at least 1 dose of DTCV but not up-to-date according to ACIP recommendations.